

**REMARKS**

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

**STATUS OF CLAIMS**

Claim 73-86 are pending. Claims 73 and 80 have been amended.

A detailed listing of all claims that were in the application is presented with an appropriate defined status identifier, regardless of whether the claims remain under examination in the application. Upon entry of this amendment, claims 73-86 will remain pending. No new matter has been added.

**1. Suspension of Prosecution**

The PAIR report for the present application contains two entries erroneously attributing suspension of prosecution to the applicants. PAIR contains an entry dated 07-06-2005 titled: "Mail Letter Suspending Prosecution at Applicant's Request" and entry dated 07-02-2005 titled: "Letter of Suspension – Applicant Initiated."

Applicants did not request a suspension of prosecution at any time and any activities that resulted in suspension was solely due to the Office's delays. Accordingly, the entries of 07-06-2005 and 07-02-2005 should be corrected to state that suspension was initiated by the Office, not Applicants.

**2. Provisional obviousness-type double patenting rejection over Application No. 09/159,105**

The Office provisionally rejected claims 73-86 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-177 of Application No. 09/159,105.

The '105 application is abandoned. Applicants submit that the rejection is moot and respectively request reconsideration and withdrawal of this rejection.

3. **Provisional rejection over U.S. 5,801,187 or 5,846,979 or 6,218,423 or 6,247,607 in view of Application No. 09/159,105 and Feghali et al.**

The Office stated “Claims 73-86 are provisionally rejected under 35 U.S.C. § 103(a) or under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the reference of the claims of Hamilton et al 5,801,187 (cited on 1449) or 5,846,979 or 6,218,423 or 6,247,607 in view of SN 09/159,105 and Feghali et al.” The Office asserts the four patents “disclosed all the elements of the claims except the neurotrophic agent.” Office Action, p. 2, para. #3.

Applicants submit that the compounds claimed in the cited patents are structurally distinct from those presently claimed and Application No. 09/159,105 is abandoned and therefore not available as prior art.

U.S. 5,801,187, U.S. 6,218,423, and U.S. 5,846,979 require a keto, carboxylic ester, or carboxamide moiety adjacent to the ring nitrogen. The compounds of the present claims do not require such a moieties.

U.S. 6,247,607 requires a  $-(C=O)-S-$  moiety or a  $-(C=S)-S-$  moiety (i.e., a thioester moiety) adjacent to the ring nitrogen. The compounds of the present claims do not require such moieties.

Accordingly, there is no overlap between the present claims and the claims of U.S. 5,801,187, or 5,846,979 or 6,218,423 or 6,247,607.

The Office applied Feghali solely for its disclosure “that sensorineural hearing loss is a neurological disorder treatable by neurotrophic factors” (Office Action, p. 2, para. 2) and consequently fails to cure the deficiencies of the primary references.

Applicants request that the Office withdraw this ground of rejection.

4. **Rejection under 35 U.S.C. § 112, second paragraph**

The Office rejected claims 73-86 for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

The Office apparently objects to the term “carboxylic acid isostere”. Independent claims 73 and 80 have been amended to delete the term “carboxylic acid isostere”. Applicants submit that the amendment obviates this ground of rejection and respectfully request withdrawal of the rejection.

**5. Rejection over U.S. 5,801,187 in view of King or Patani**

Claims 73-86 are rejected under the judicially created doctrine of obviousness-type double patenting over claim 9-12 of U.S. 5,801,187 in view of King or Patani. Applicants respectfully traverse.

First, the compounds of the '187 patent require carboxylic esters, whereas the instant compounds do not require such a moiety. The Office states that “the claims included both the “carboxylic acid” isosteres and the “carboxylate” isosteres.” Applicants respectfully submit that instant claims do not encompass carboxylate isosteres.

As to the relevance of the King and Patani references, the Office apparently relies on these references to support the premise that “modified compounds under the bioisosterism principle is well recognized to have the same utility as the lead compound” (Office Action, p. 4, ll. 7-9).

Applicants respectfully submit that the King and Patani references themselves contradict the Office’s assertion by casting doubt on the predictability of success in bioisosteric replacement. Far from disclosing the bioisosteric groups are interchangeable in drugs to retain identical pharmaceutical activity, these references present the biosisosterism principle as an alternative “rational” drug discovery strategy. Specifically, these references state:

Three of the standard methodologies that the medicinal chemist can use as “rational” approaches to lead optimization form the basis of this chapter. These are bioisosteric replacement, conformational restriction, and pro-drug formation.

...

Bioisosteres, however, are substituents or groups that do not necessarily have the same size or volume, but have a similarity

in chemical or physical properties which produce broadly similar biological properties. It is therefore unlikely that bioisosterism will produce marked increases in potency; however **significant changes in selectivity, toxicity, and metabolic stability could be expected.**

...

When considering any approach to lead optimization, alteration of one part of the molecule almost always affects more than just one property. Isosteric and bioisosteric replacements are no exception and this should always be considered when analyzing the result of such replacements. For example a simple CH<sub>2</sub> to O to S series of replacements can alter size, shape, electronic distribution, water or lipid solubility, pK<sub>a</sub>, metabolism, or hydrogen bonding capacity, all with **unpredictable effects upon biological activity.**

King, p. 207, ll. 12-15 and 28-32, and p. 209, ll. 1-7.

Bioisosterism represents one approach used by the medicinal chemist for the rational modification of lead compounds into safer and more clinically effective agents. **The concept of bioisosterism is often considered to be qualitative and intuitive.**

...

As can be the case for any bioisostere, not all of these replacements will necessarily result in a compound with comparable biological activity to the template drug.

Patani, p. 3147, left col. l. 2 from bottom, to right col., l. 4, and p. 3165, left col. ll. 21-24.

Asserting obviousness based on speculative bioisosterism alone is a classic example of applying the impermissible “obvious to try” standard of obviousness. *In re O’Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) (what would have been “obvious to try” would have been . . . to vary all parameters or try each of numerous possible choices . . . where the prior art gave . . . no direction as to which of many possible choices is likely to be successful [or] . . . to explore . . . a promising field of experimentation, where the prior art gave only general guidance). *See In re Merck & Co.*, 800 F.2d 1091 (Fed. Cir. 1986) (structural similarity, prior

art suggestion of claimed anti-depressant activity of claimed compounds, and a suggested bioisosteric relationship together yield a *prima facie* case of obviousness).

Here, the compounds are not structural similar, there is no prior art suggestion of activity of the claimed compounds, and there is a tenuous “non-classical” bioisosteric relationship in the relevant moieties.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection under § 103 (a).

**6. Ownership of applications**

The Examiner requested clarification of the ownership of the present application and Application No. 09/159,105 (national phase of PCT application WO 99/14998). This issue is now moot because, as noted above, Application No. 09/159,105 is abandoned.


**CONCLUSION**

Applicants believe that entry of this amendment would place the present application in condition for allowance entry. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the application to allowance.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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By 

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